

## Supplementary Online Content

Andrén Aronsson C, Lee H-S, Hård af Segerstad EM, et al, for the TEDDY Study Group. Association of gluten intake during the first 5 years of life with incidence of celiac disease autoimmunity and celiac disease among children at increased risk. *JAMA*. doi:10.1001/jama.2019.10329

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Daily gluten intake (gram per day) at clinic visits by country

	<b>USA</b> n = 2644		<b>Finland</b> n = 1508		<b>Germany</b> n = 384		<b>Sweden</b> n = 2069	
Visits (months)	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
6	0.08	0.23	0.29	0.50	0.40	0.62	0.53	0.66
9	0.62	0.74	1.13	0.96	1.48	1.33	1.79	0.98
12	1.65	1.19	2.13	1.37	3.13	1.94	2.88	1.38
18	2.76	1.54	3.48	1.78	4.63	2.08	3.67	1.38
24	3.20	1.72	4.01	1.84	5.21	2.15	3.93	1.45
30	3.59	1.84	4.54	2.00	5.97	2.72	4.17	1.58
36	3.84	1.82	4.87	1.86	6.07	2.26	4.45	1.65
42	4.20	1.97	5.33	2.15	6.63	2.34	4.76	1.70
48	4.53	2.02	5.61	2.13	7.10	2.78	4.96	1.82
54	4.90	2.10	5.98	2.12	8.43	2.63	5.34	1.93
60	5.06	2.23	6.35	2.22	8.58	3.28	5.60	1.86

**Footnote:** Gluten intake was considered up to the last visit prior to seroconversion to positive tTGA autoantibodies (leading to celiac disease autoimmunity) or last date of follow-up.

**eTable 2.** Non-dietary risk factors for celiac disease autoimmunity and celiac disease

	Celiac disease autoimmunity		Celiac disease	
	HR (95% CI)	p-value	HR (95% CI)	p-value
<b>HLA-genotype</b>				
HLA others	1		1	
DR3-DQ2/DR4-DQ8	2.07 (1.77 to 2.42)	<.001	1.88 (1.42 to 2.48)	<.001
DR3-DQ2/DR3-DQ2	4.97 (4.25 to 5.82)	<.001	5.75 (4.40 to 7.50)	<.001
<b>Country</b>				
USA	1		1	
Finland	1.13 (0.97 to 1.33)	0.12	1.18 (0.89 to 1.57)	0.25
Germany	1.01 (0.77 to 1.33)	0.94	0.98 (0.59 to 1.65)	0.96
Sweden	1.36 (1.19 to 1.54)	<.001	2.14 (1.72 to 2.66)	<.001
<b>Sex</b>				
Male	1		1	
Female	1.56 (1.39 to 1.75)	<.001	1.94 (1.60 to 2.35)	<.001
<b>First degree relative with celiac disease</b>				
No	1		1	
Yes	2.45 (2.03 to 2.95)	<.001	3.96 (3.08 to 5.09)	<.001

**eTable 3.** Daily gluten intake and risk for developing celiac disease autoimmunity and celiac disease by study site and country

		Celiac disease autoimmunity		Celiac disease	
Country	Measurements of gluten	HR <sup>a</sup> (95% CI)	p-value	HR <sup>a</sup> (95% CI)	p-value
USA, n=444 <sup>c</sup>	Absolute intake (g/day)	1.32 (1.20 to 1.46)	<.001	1.71 (1.44 to 2.02)	<.001
	Residual intake (g/day) <sup>b</sup>	1.37 (1.22 to 1.54)	<.001	1.45 (1.14 to 1.85)	0.003
	Intake /10 kg body weight	1.85 (1.53 to 2.23)	<.001	2.90 (2.04 to 4.11)	<.001
Colorado, n=194	Absolute intake (g/day)	1.29 (1.11 to 1.50)	0.001	1.83 (1.42 to 2.34)	<.001
	Residual intake (g/day) <sup>b</sup>	1.23 (1.02 to 1.48)	0.03	1.46 (1.05 to 2.05)	0.03
	Intake /10 kg body weight	1.57 (1.18 to 2.09)	0.002	2.84 (1.77 to 4.55)	<.001
Georgia/Florida, n=108	Absolute intake (g/day)	1.27 (1.04 to 1.54)	0.02	1.29 (0.84 to 1.99)	0.25
	Residual intake (g/day) <sup>b</sup>	1.38 (1.10 to 1.72)	0.005	0.89 (0.49 to 1.63)	0.71
	Intake /10 kg body weight	2.00 (1.34 to 3.00)	<.001	1.43 (0.54 to 3.80)	0.47
Washington, n=141	Absolute intake (g/day)	1.45 (1.23 to 1.71)	<.001	1.79 (1.28 to 2.51)	<.001
	Residual intake (g/day) <sup>b</sup>	1.63 (1.32 to 2.02)	<.001	2.04 (1.30 to 3.19)	0.002
	Intake /10 kg body weight	2.14 (1.54 to 2.99)	<.001	3.10 (1.61 to 5.96)	<.001
Finland, n=251	Absolute intake (g/day)	1.29 (1.13 to 1.48)	<.001	1.24 (0.95 to 1.62)	0.12
	Residual intake (g/day) <sup>b</sup>	1.44 (1.22 to 1.70)	<.001	1.34 (0.95 to 1.88)	0.09
	Intake /10 kg body weight	1.65 (1.30 to 2.11)	<.001	1.46 (0.90 to 2.37)	0.12
Germany, n=57	Absolute intake (g/day)	1.18 (0.97 to 1.43)	0.09	n.a.	
	Residual intake (g/day) <sup>b</sup>	1.46 (1.11 to 1.93)	0.01	n.a.	
	Intake /10 kg body weight	1.56 (1.04 to 2.35)	0.03	n.a.	
Sweden, n=464	Absolute intake (g/day)	1.53 (1.32 to 1.77)	<.001	1.83 (1.48 to 2.26)	<.001
	Residual intake (g/day) <sup>b</sup>	1.53 (1.29 to 1.82)	<.001	1.58 (1.18 to 2.10)	0.002
	Intake /10 kg body weight	1.80 (1.36 to 2.40)	<.001	1.45 (0.93 to 2.25)	0.10

<sup>a</sup> Joint modeling adjusted for HLA-type, sex, first degree relative with celiac disease, and energy intake

<sup>b</sup> Age- and energy adjusted intake using the residual model <sup>(ref 27)</sup>

<sup>c</sup> Seven participants (including one participant with celiac disease autoimmunity) were followed at a US satellite clinic outside the main US study sites, and were not included in the site specific analyses.

n = Number of children with celiac disease autoimmunity included in each analysis.

**eTable 4.** Daily absolute gluten intake reported at the 2 and 3 year study visits and risk for developing celiac disease autoimmunity and celiac disease

TEDDY visit	Model <sup>a</sup>	Gluten intake	Celiac disease autoimmunity		Celiac disease	
			HR (95% CI)	p-value	HR (95% CI)	p-value
2 years	A n=171	At 2 years; same as the most recent prior to event,	1.30 (1.19 to 1.42)	<.001	1.35 (1.17 to 1.56)	<.001
	B n=662	At 2 years	1.05 (1.01 to 1.10)	0.03	1.12 (1.04 to 1.22)	0.004
		The most recent intake prior to event	1.08 (1.04 to 1.13)	<.001	1.02 (0.95 to 1.10)	0.62
3 years	A n=133	At 3 years; same as the most recent prior to event	1.20 (1.09 to 1.32)	<.001	1.07 (0.91 to 1.26)	0.41
	B n=393	At 3 years	1.02 (0.97 to 1.08)	0.42	1.05 (0.95 to 1.15)	0.37
		The most recent intake prior to event	1.06 (1.00 to 1.11)	0.04	1.00 (0.91 to 1.11)	0.93

Model A: include children with gluten intake at the specific age as the most recent intake prior to the event.

Model B: include children with additional gluten intake after the specific age but prior to the event.

<sup>a</sup> Both models are adjusted for HLA-type, country, sex, first degree relative with celiac disease, and energy intake at the age of gluten intake.

n: Number of children with Celiac disease autoimmunity included in each model.

**eTable 5.** Daily absolute gluten intake reported at the 2-year study visit and risk for developing celiac disease autoimmunity and celiac disease

	Model A			Model B		
	HR (95% CI)		p-value	HR (95% CI)		p-value
	≤ 2g/day	> 2g/day		≤ 2g/day	> 2g/day	
<b>Celiac disease autoimmunity</b>	1	1.49 (1.16 - 1.91)	0.002	1	1.62 (1.29 - 2.03)	<.001
<b>Celiac disease</b>	1	1.75 (1.10 - 2.81)	0.02	1	1.71 (1.12 - 2.60)	0.01

A: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake and the most recent gluten intake prior to the event as time dependent covariates

B: Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2-year study visit.

Abbreviation: FDR; first degree relative

**eTable 6.** Daily absolute gluten intake reported at the 2-year study visit and risk for developing celiac disease autoimmunity and celiac disease

	HR	HR (95% CI) <sup>a</sup>	p-value	HR (95% CI) <sup>a</sup>	p-value	HR (95% CI) <sup>a</sup>	p-value	HR (95% CI) <sup>a</sup>	p-value
	≤2g/day <sup>b</sup>	>2 and ≤4g/day <sup>b</sup>		>4 and ≤6g/day <sup>b</sup>		>6 and ≤8g/day <sup>b</sup>		> 8 g/day <sup>b</sup>	
<b>Absolute intake (g/day), mean (SD)</b>	1.4 (0.5)	3.0 (0.6)		4.8 (0.6)		6.8 (0.5)		9.3 (1.4)	
<b>Celiac disease autoimmunity</b>	1	1.52 (1.20-1.93)	<.001	1.77 (1.37-2.29)	<.001	2.43 (1.76-3.36)	<.001	1.54 (0.81-2.93)	0.70
<b>Celiac disease</b>	1	1.57 (1.02-2.41)	0.04	1.96 (1.24-3.11)	0.004	2.69 (1.53-4.71)	<.001	2.04 (0.68-6.08)	0.20

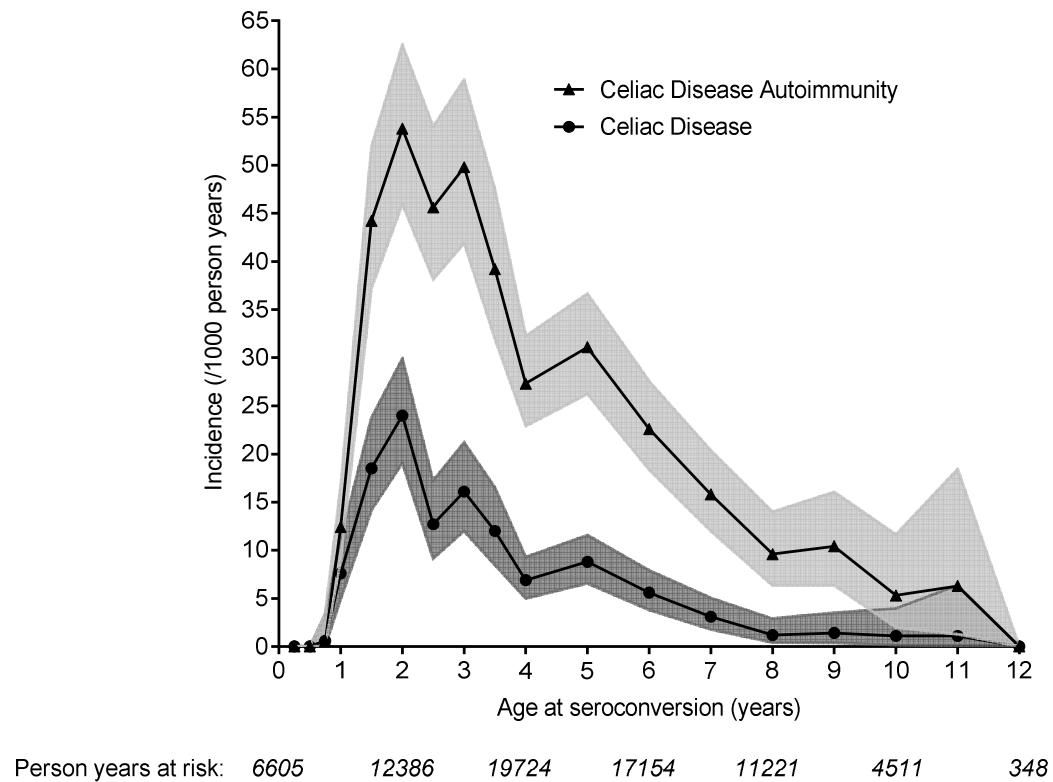
<sup>a</sup> Adjusted for HLA-type, country, sex, FDR with celiac disease, and energy intake at 2 year study visit

<sup>b</sup> Number of children with Celiac disease autoimmunity included in each model; ≤2g/day: 90 (11%), >2 and ≤4g/day: 392 (47%), >4 and ≤6g/day: 259 (31%), >6 and ≤8g/day: 81 (10%), > 8 g/day: 11 (1%)

Abbreviation: first degree relative; FDR



**eFigure 1.** Incidence of seroconversion to celiac disease autoimmunity and celiac disease over time



Median (IQR) observation time for both celiac disease autoimmunity and celiac disease was 9 year (Q1: 8 years, Q3: 10 years). Line denote the mean and filled area 95% confidence interval.

**eFigure 2.** Martingale residual plots and local linear regression (LOESS line; blue line) for absolute gluten intake (g/day) at the 2 year study visit from the Cox regression model

